Remarks

By this amendment, claims 19 and 21-35 are pending. Claim 20 has been cancelled. Claims 19, 32, 33 and 35 have been amended. Claims 36 and 37 have been newly added. Support for these amendments is found in the specification at paragraphs 21, 23 and 30. Claims 27, 29, 30, 34 and 35 have also been amended to correct the dependencies from the Examiner's renumbering of the claims in the Office Action dated April 20, 2006. No new matter is added with these amendments.

Summary of Interview with Examiner

Applicants wish to thank the Examiner for her time and consideration during the personal interview with the applicant's representatives, John McDonald and Stephen MacDonald, on August 8, 2006. During the interview, applicants discussed prospective amendments to the claims and the differences between the claimed method and the prior art (Uki et al. *Jpn J. Alcohol & Drug Dependence*, 1994; Derlet et al. *Neuropharmacology*, 1990; Gasior et al. *J. Pharmacol Exp Therap*, 2000; Yelle US Patent 6,468,997B2; and Wolf, Cocaine Poisoning, *Clinical Toxicology Review*, 1995).

As indicated on the Interview Summary, the Examiner understood that Uki et al and Derlet et al. are directed to treatment of cocaine poisoning whereas the claimed method is directed to treating cocaine dependency.

Double Patenting

Claims 19-35 were provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 14, 16, 17, 19, 20-27 and 29 of co-pending

application 11/111,435 in view of Hadcock (US Patent No. 6,451,783B1). Applicant respectfully requests the deferral of this rejection until such time that allowable subject matter is found in both applications.

Rejections under 35 U.S.C. §112, first paragraph (enablement)

Claims 32 and 35 have been rejected under 35 U.S.C. §112, first paragraph as lacking enablement for the term "eliminating desire to use cocaine". Applicant respectfully traverses this rejection as it applies to the claims as amended.

Applicant has amended claims 32 and 35 to remove the term "eliminating" and therefore respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. §112, second paragraph

Claim 20 has been rejected under 35 U.S.C. §112, second paragraph for being indefinite. Applicant has cancelled claim 20 without prejudice thereby rendering this rejection moot.

Rejections under 35 U.S.C. §102

Claims 19, 26, 28 and 32 have been rejected under 35 U.S.C. §102(b) as being anticipated by Uki et al. (*Jpn J. Alcohol & Drug Dependence*, 1994, hereinafter "Uki"). Applicant respectfully traverses the rejection.

Uki Discloses Protection from Cocaine Poisoning, not Treatment of Dependency

The Examiner asserts that Uki discloses a treatment of cocaine abuse and dependency with flumazenil however, Uki administers flumazenil immediately after administration of a toxic bolus of cocaine in order to delay the onset of seizures and death. Uki is therefore employing a model of cocaine poisoning and not cocaine dependency. Cocaine poisoning and cocaine dependency are very different conditions. Referring to the article by Woolf et al., cited by the Examiner in the instant Office Action, treatment of cocaine poisoning requires intensive supportive care which may include i.v. fluid administration, activated charcoal administration, and pharmacological prevention of cardiac events, seizures and life-threatening hyperthermia. (see Woolf, page 4). Conversely, treatment of cocaine dependency does not include such measures.

Uki prophylactically administers flumazenil immediately after cocaine insult and before the onset of action of cocaine as a protective measure to reduce the occurrence of a cardiac or seizure event. Uki does not disclose a treatment of cocaine dependency. Cocaine dependency is a chronic condition associated with an individual taking non-lethal amounts of cocaine. Uki's animal model fails to represent a model of dependency since the cocaine dose kills the rats.

A Cocaine Dependent Individual Would Not Experience the Cocaine Levels Described in Uki

The amount of cocaine administered in Uki creates a model of cocaine poisoning and greatly exceeds the amount that would be used by an individual with cocaine dependency. Uki discloses administration of cocaine at a concentration of 70 mg/kg. This dosage would

be equal to 4.9 grams in an average human weighing 70 kg. The lethal dose of cocaine for a human is an oral dose of 1-3 grams or 750-800 mg by i.v. administration. (Woolf et al., page 2). Therefore the cocaine dose disclosed in Uki exceeds the human lethal dose by 2-7 times. Uki describes an animal model for an entirely different clinical situation and is therefore non-analogous to the claimed method of treating cocaine dependency.

Uki teaches that cocaine toxicity is from administration of one large dose of cocaine that induces seizures and death. In contrast, cocaine dependency results from the chronic use of much smaller cocaine doses that do not cause seizures and death. The pending claims are directed to methods of treatment of cocaine dependency, not toxicity. Dependency and toxicity are two entirely different conditions and therefore the claimed method to treat dependency is not anticipated by Uki. Uki provides no teaching to treat cocaine dependency.

Uki Fails to Disclose the Same Therapeutically Effective Amount of Flumazenil

Uki discloses the administration of flumazenil between 0.125 mg/kg to 1.0 mg/kg. For an average 70 kg human, these doses are extrapolated to 4.4 mg to 70.0 mg of flumazenil and greatly exceed the therapeutically effective amount of flumazenil that is taught by the specification for treating cocaine dependency.

In view of the preceding comments, Uki relates to an entirely different clinical situation, fails to teach treatment of cocaine dependency, fails to disclose the same effective amount of flumazenil and therefore fails to anticipate the claimed methods. Applicant respectfully requests withdrawal of this rejection.

Rejections under 35 U.S.C. §103

Claims 20-25, 27, 33 and 34 have been rejected under 35 U.S.C. §103(a) as being obvious over Uki et al. in view of Derlet et al. (Neuropharmacology, 1990, hereinafter "Derlet"). Applicant respectfully traverses the rejection.

Uki has been described above.

Derlet Also Discloses Prevention of Cocaine Poisoning Not Dependency

Much like Uki, Derlet disclose the use of a rat model to study the actions of known drugs to preemptively protect the rat from acute, cocaine-induced *toxicity* that causes seizures and death. Similarly, the amount of cocaine administered in Derlet for toxicity is very high and greatly exceeds the amount that would be used by an individual with cocaine dependency. Derlet disclose administration of cocaine at a concentration of 70 mg/kg. This dosage would be equal to 4.9 grams in an average human weighing 70 kg. The lethal dose of cocaine for a human is an oral dose of 1-3 grams or 750-800 mg by i.v. administration. (Woolf et al., page 2). Therefore the cocaine dose disclosed in Derlet exceeds the human lethal dose by 2-7 times.

Flumazenil is Administered before Cocaine Administration

The claims are directed to treating cocaine *dependency* with flumazenil. Cocaine toxicity (i.e. cocaine poisoning) and dependency are very different conditions. Derlet disclose that flumazenil and other drugs are administered intraperitoneally (i.p.), 30 min before administration of cocaine to protect from cocaine intoxication. (Derlet, page 255). The prophylactic use of flumazenil before cocaine administration fails to approximate a model of cocaine dependency since the amount of cocaine administered to the rats is lethal. In

addition, this is the first occasion the rats have been administered cocaine. Dependency can not exist without prior exposure to cocaine.

In contrast, the present claims are directed to a method for treating cocaine dependency using flumazenil. Cocaine dependency results from the frequent use of much lower cocaine doses that do not cause seizures and death. Derlet disclose on page 257 that their rat model of cocaine toxicity "better simulates the clinical setting of an acute overdose in humans". As such, the animal model disclosed in Derlet fails to approximate a model for cocaine dependency.

Derlet Fails to Disclose the Same Therapeutically Effective Amount of Flumazenil

Derlet administers flumazenil between 5 mg/kg and 20 mg/kg. If this amount were extrapolated to an average 70 kg individual, this would amount to between 350 mg and 1400 mg of flumazenil which grossly exceeds the therapeutically amount of flumazenil to treat dependency as taught by the specification. One of ordinary skill would not arrive at Applicant's claimed therapeutically effective amount of flumazenil to treat dependency absent the teachings of the present specification.

Derlet fails to make up for the deficiencies of Uki and therefore fails to render the claimed methods obvious. Neither Uki or Derlet alone, or in combination provide any teaching, suggestion of provide motivation to arrive at the Applicant's claimed method. Therefore, the Applicant respectfully requests withdrawal of this rejection.

Claim 29 has been rejected under 35 U.S.C. §103(a) as being obvious over Uki et al. in view of Gasior et al. (*J. Pharmacol Exp Therap*, 2000, hereinafter "Gasior"). Applicant respectfully traverses the rejection.

Uki has been discussed above.

Gasior

Gasior is cited for the technical feature of co-administering clomethiazole as an additional agent. Gasior fails to make up for the deficiencies of Uki in treating cocaine dependency with an effective amount of flumazenil and therefore fails to render the claimed methods obvious. Neither Uki or Gasior alone, or in combination provide any teaching, suggestion of provide motivation to arrive at the Applicant's claimed method. Applicant respectfully requests withdrawal of this rejection.

Claim 30 has been rejected under 35 U.S.C. §103(a) as being obvious over Uki et al. in view of Yelle et al. (U.S. Patent No. 6,468,997B2, hereinafter "Yelle"). Applicant respectfully traverses the rejection.

Yelle

Yelle is cited for the technical feature of co-administering fluoxetine as an additional agent. Yelle fails to make up for the deficiencies of Uki in treating cocaine dependency with an effective amount of flumazenil and therefore fails to render the claimed methods obvious. Neither Uki or Yelle alone, or in combination provide any teaching, suggestion of provide motivation to arrive at the Applicant's claimed method. The Applicant respectfully requests withdrawal of this rejection.

Claim 31 has been rejected under 35 U.S.C. §103(a) as being obvious over Uki et al. in view of Woolf (Cocaine Poisoning, Clinical Toxicology Review, 1995, hereinafter "Woolf"). Applicant respectfully traverses the rejection.

Woolf

Woolf is being cited for the technical feature of administering a cocaine poisoning treatment under sedation. Woolf fails to make up for the deficiencies of Uki in treating cocaine dependency with an effective amount of flumazenil and therefore fails to make the claimed methods obvious. The Applicant respectfully requests withdrawal of this rejection.

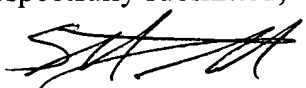
Conclusion

Applicant submits that the pending claims define novel and patentable subject matter and provide a complete response to the Office Action. Accordingly, Applicant respectfully requests allowance of these claims. A Form PTO-2038 is enclosed for the $60.00 fee for a one-month Extension of Time for a small entity; however, the Commissioner is hereby authorized to charge any deficiencies which may be required, or credit any overpayment, to Deposit Account Number 11-0855.

Early and favorable consideration is earnestly solicited. If the Examiner believes any informalities remain in the application that can be resolved by telephone interview, a telephone call to the undersigned is earnestly solicited.

Allowance of claims 19 and 21-35 is respectfully solicited.

Respectfully submitted,



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Attorney Docket: 55979-0200US (314570)